Provincial Health Services Authority

Protocol number v12.0; 16 Apr 2024

Protocol Title: A Randomized Phase III Trial Comparing Simple Unplanned Palliative Radiotherapy versus 3D Conformal Radiotherapy for Patients with Bone Metastases

Protocol Number: 18-25

Version Number: 12.0

Study Phase: 3

Short Title: SUPR-3D

Sponsor Name:

[BC Cancer – Prince George

1215 Lethbridge St., Prince George, BC, V2M 7E9]

.

[Version 1.0: 10 JUL 2018

Version 2.0: 14 JAN 2019

Version 3.0: 26 MAR 2019

Version 4.0: 01 JUN 2019

Version 5.0: 27 July 2019

Version 6.0: 11 Dec 2019

Version 7.0: 09 Jun 2020

Version 8.0: 10 Jun 2020

Version 9.0: 17 Mar 2021

Version 10.0: 13 Apr 2022

Version 11.0: 01 Jun 2023]

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I. Signature of Principal Investigator

I agree to the terms of this clinical trial protocol and all amendments. I will conduct the trial in compliance with all stipulations of the protocol, according to the principles of ICH Good Clinical Practice (GCP) and any applicable local regulations.

(see electronic signature)

Dr. Robert Olson	Date

II. Contact Details of Key Personnel

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III. LIST OF ABBREVIATIONS

Abbreviations	Description of Abbreviations
AAA	Analytical Anisotropic Algorithm
AE	Adverse event
AP:PA	Anterior-Posterior: Posterior-Anterior
BPI	Brief Pain Inventory
CBCT	Cone-Beam CT
CI	Conformity Index
CR	Complete response
(e)CRF	(Electronic) Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
Dmax	Maximum Dose
DSMC	Data Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EORTC	European Organisation for Research and Treatment of Cancer
EQD2	Equivalent Dose in 2 Gy fractions
FLIE	Functional Living Index - Emesis
GCP	Good Clinical Practice
GTV	Gross Tumour Volume
HCP	Health Care Provider
HRQoL	Health Related Quality of Life
ICF	Informed consent form
ICH	International Council for Harmonization

IGRT	Image Guided Radiation Therapy
IRB	Institutional Review Board
KT	Knowledge Translation
kV	Kilo-Volt
MF	Multi Fraction
MLC	Multi-Leaf Collimator
OAR	Organ At Risk
OMED	Oral Morphine Equivalent Dose
PI	Principal Investigator
PR	Partial response
PRO	Patient Reported Outcome
PROMS	Patient Reported Outcome Measures
PTV	Planning Target Volume
QA	Quality Assurance
QALY	Quality Adjusted Life Year
QoL	Quality of Life
QUANTEC	Quantitative Analyses of Normal Tissue Effects in the Clinic
REB	Research Ethics Board
RINV	Radiation-Induced Nausea and Vomiting
RO	Radiation Oncologist
RT	Radiation Therapy
SAE	Serious adverse event
SF	Single Fraction
SFRT	Stereotactic Fractionated Radiotherapy
SOP	Standard Operating Procedure
SPI	Study Principal Investigator

SUPR	Simple Unplanned Palliative Radiation
VMAT	Volumetric Modulated Arc Therapy

1. Protocol Summary

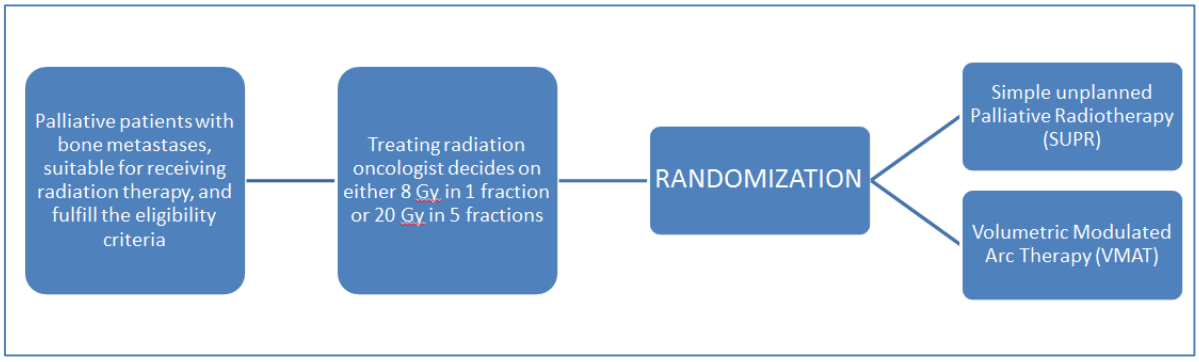
Date and Version # of Protocol:	16 Apr 2024; v12.0
Sponsor: BC Cancer	**Protocol Number:** 18-25
Name of Study Method: Randomized Controlled Clinical Trial	**Phase of Development:** III

Title of Study:

A Randomized Phase III Trial Comparing Simple Unplanned Palliative Radiotherapy versus 3D Conformal Radiotherapy for Patients with Bone Metastases.

Study Design Overview/Rationale:

The primary objective is to compare patient-reported Quality of Life related to Radiation Induced Nausea and Vomiting (RINV) between standard palliative radiotherapy and VMAT. Secondarily, we will assess rate of complete control of RINV, compare patient reported toxicity, and evaluate pain response. However, we hypothesize that there will be no difference in pain response between the two arms, because they are receiving the same dose.



Trial Design and Schema

This is a randomized, multi-centre, pragmatic phase III study in palliative patients with bone metastases.

Randomization will be performed on patient-level, meaning that if a patient is treated for multiple bone metastases in the same course, all will receive the same treatment technique.

This applies only to bone lesions, as per section 3.2. Any additional lesions to be treated will be at the RO's discretion.

Stratification: 8 Gy/1 vs 20 Gy/5

Radiation Treatment Plan (Arm 1):

Location	Dose (Gy)	Fractions	Frequency
Bone metastasis	8	1	Single fraction
Bone metastasis	20	5	Once daily

Radiation Treatment Plan (Arm 2):

Location	Dose (Gy)	Fractions	Frequency
Bone metastasis	8	1	Single fraction
Bone metastasis	20	5	Once daily

Disease Assessment:

- Patient Reported Quality of life related to RINV as scored by the Functional Living Index – Emesis (FLIE)
- Control of RINV as measured by a daily patient diary
- Patient reported pain response as measured by the Brief Pain Inventory (BPI)
- Patient reported use of medications as measured by patient diary
- Patient reported fatigue, nausea, vomiting as measured by the PRO-CTCAE
- Patient reported quality of life as measured by EORTC QLQ C-15 PAL
- Patient reported functional status as measured by PRO-ECOG
- Economic analysis as measured by EQ-5D-5L

Study Population

Patients with a clinical diagnosis of bone metastases, meeting all inclusion and exclusion eligibility criteria.

Study Objective(s):

Primary Objective

The primary objective is to compare patient-reported Quality of Life related to Radiation Induced Nausea and Vomiting (RINV) between standard palliative radiotherapy and VMAT.

Secondary Objective:

To assess rate of complete control of RINV, compare patient reported toxicity, and evaluate pain response. However, we hypothesize that there will be no difference in pain response between the two arms, because they are receiving the same dose.

Number of Subjects/Sample Size Calculations

250 subjects will be accrued

Planned Study Period:

7 Years

Inclusion Criteria:

Subjects must meet all of the following criteria to be eligible for participation in this study:

- Age 18 or older
- Able to provide informed consent
- Clinical diagnosis of cancer with bone metastases (biopsy not required)
- Currently being managed with palliative intent RT to 1-3 RT fields for bone metastases, at least one RT field (PTV) must (at least) partly lie within T11-L5 or pelvis.
- ECOG Performance Status 0-3
- Patient has been determined to potentially benefit from 8 Gy or 20 Gy
- Radiation Oncologist is comfortable prescribing 8 Gy in 1 fraction or 20 Gy in 5 fractions RT for bone metastases
- Negative pregnancy test result for women of child-bearing potential
- The baseline assessment must be completed within required timelines, prior to randomization.
- Patients must be accessible for treatment and follow-up. Investigators must assure themselves the patients randomized on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.
- For simplicity of planning, expected GTV should be less than 20 cm based on radiological or clinical evidence

- Patient must be prescribed a 5-HT3 receptor antagonist (e.g. Ondansetron) as antiemetic prophylaxis prior to RT start.
- Patient is able and willing to complete the quality of life questionnaires, and other assessments that are a part of this study, via paper or using REDCap if they provide their email address on the informed consent

Waivers to the inclusion criteria will NOT be allowed.

Exclusion Criteria:

Subjects are excluded from the study if any of the following criteria apply:

- Serious medical co-morbidities precluding radiotherapy
- Clinical evidence of spinal cord compression
- Spinal cord in treatment field has already received at least >30 Gy EQD2, defined as:
  $EQD_2 = D \times ([d + (\alpha/\beta)]/[2 + (\alpha/\beta)])$
  D = total dose given in Gy
  d = dose per fraction in Gy
  α/β = dose at which the linear and quadratic components of cell kill are equal
- Whole brain radiotherapy (WBRT) within 4 weeks of RT start or planned WBRT in the first 4 weeks after last RT
- Solitary plasmacytoma
- Pregnant or lactating women
- Target volume cannot be encompassed by a single VMAT isocentre
- Custom mould room requirements (shells and other immobilization that is standard-of-care is acceptable)
- Greater than two organs-at-risk requiring optimization.
- Patients requiring treatments outside standard clinical hours
- Implanted electronic device within 10 cm of the RT fields
- Prostheses in the axial plane of the target, or within 1 cm of the PTV out-of-plane
- Previous RT that requires an analysis of cumulative dose (i.e. sum plans or EQD2 calculations)
- Oral or IV contrast if the local standard-of-care requires compensation for this in planning.

Waivers to the exclusion criteria will NOT be allowed.

Concomitant Medication Restrictions or Requirements:

Required/Permitted:

- Antiemetic prophylaxis with 5-HT3 receptor antagonist (e.g. Ondansetron) prescribed before start of RT
- Analgesics can be prescribed as needed
- Concurrent hormonal therapy is allowed

Restrictions:

- Use of chemotherapy schemes containing potent enhancers of radiation damage (e.g. gemcitabine, doxorubicin, bevacizumab, adriamycin) are **discouraged within the first month after radiation**.
- WBRT in the 4 weeks before first RT and 4 weeks after last RT
- SFRT for brain metastases in the 4 weeks after last RT

Schedule of Study Assessments and Procedures:

For Schedule of Assessments refer to Section 4.8

Adverse Events Determination and Reporting:

Grade 1 toxicities such as mild fatigue, nausea, vomiting, skin irritation, pain, loss of appetite and some physical function are common and expected side effects of radiation therapy and therefore should not be reported as adverse events, if the event is documented in the subject's medical record. Only Grade 2 or higher toxicities that are possibly, probably, or definitely related to RT will be documented and reported as adverse events (AEs)/serious adverse events (SAEs).

Any **Grade 4 or 5 serious adverse event** that is definitely, probably, or possibly the result of protocol treatment must be reported to the Study PI within 24 hours of discovery. The follow-up/final report should be completed within an additional 8 days. All other SAEs (Grade 2-3) that are definitely, probably, or possibly related to treatment should be reported to the Study PI within 15 days. These should be documented in an SAE Report form and in REDCap as well.

Unanticipated events are to be reported to the Study PI within 24 hours of discovery, and to the local REB as required.

Local and non-local SAEs will be reported to the applicable REB as per their reporting guidelines.

NOTE: Conditions that are NOT considered a SAE in this protocol are not included in reporting requirements, e.g., hospitalizations for routine procedures, disease progression, or death from disease progression.

Formal Stopping Rules:

The primary objective of this study is to compare patient-reported QoL related to RINV between SUPR and VMAT. Accruing 250 patients will increase confidence in improved QoL of VMAT (i.e. lower RINV as measured by FLIE).

There is no independent data safety monitoring committee (DSCM) for this study. The DSMC will be made up of the study co-investigators. The DSMC will meet annually after study initiation to review toxicity outcomes. If any grade 3-5 toxicity is reported, the DSMC will review the case notes to determine if such toxicity is related to treatment. If the DSMC deems that toxicity rates are excessive (>25% grade 3 toxicity or >10% grade 4 or >3% grade 5 toxicity), then the DSMC can, at its discretion, recommend cessation of the trial, dose adjustment or exclusion of certain treatment sites that are deemed as high-risk for complications.

Statistical Evaluations:

Patients will be analyzed in the groups to which they are assigned (intention-to-treat).

RINV will be assessed via Functional Living Index – Emesis (FLIE) scores compared between the two arms at baseline and day 5 post start of RT

Health-Related Quality of Life (HRQoL) will be measured using the EQ-5D-5L and combined with survival outcomes to explore differences in Quality Adjusted Life Year (QALY) gains or losses between treatments

Endpoints for Evaluation:

- Patient Reported Quality of life related to RINV as scored by the Functional Living Index – Emesis (FLIE)
- Toxicity as scored by Patient Reported Outcome Measures (PROMs)
- Health-related quality of life as measured by the EQ-5D-5L and combined with survival outcomes to explore differences in QALY gains or losses between treatments

2. Introduction

2.1. Trial Rationale and Background

Bone metastases are the most common site of distant metastases and can cause severe and disabling effects, including pain, spinal cord compression and pathologic fracture[1, 2]. These complications can greatly affect a patient's quality of life and cause immense suffering.

Radiotherapy (RT) is an effective treatment for palliative patients with painful bone metastases. It is also efficacious in preserving function and maintaining skeletal integrity, while minimizing the occurrence of adverse skeletal related events[3]. There is a significant amount of evidence showing that a single fraction (SF) of RT provides equivalent pain relief as multiple fractions (MF), which are associated with more acute toxicity, are less convenient for patients and costlier for the health care system[1, 4, 5]. Therefore, SF-RT is encouraged, but 20 Gy in 5 fractions is also allowed in this study, though should be chosen only in patients with a complicated bone metastases by fracture, neurological deficit (e.g. spinal cord compression), or a large soft tissue component. In patients with advanced disease, management strategies focus on improving quality of life (QOL), rather than conventional endpoints such as survival[6].

Rationale for Current Study

Currently, the standard of care in British Columbia for palliative patients with bone metastases is SUPR. In other jurisdictions, however, factors such as physician remuneration make other complex planning techniques more popular.

BC Cancer is publicly funded with no direct costs to patients. All RT in the province is provided by 6 centres where radiation oncologists receive an annual salary, which are independent of RT treatment technique and duration[7]. Due to the lack of financial incentive associated with a more complex RT plan, BC Cancer is a unique clinical setting to assess the use of VMAT versus SUPR[7].

As facilities providing RT have gained more experience with VMAT and improvements to VMAT planning software have been made, the planning time required has been reduced[8]. Previously, approximately 2 weeks was required for a team at the BC Cancer to create a VMAT plan for a palliative patient with bone metastases; however, we hypothesize this can now be reduced to three days in settings with low dose prescription.

This study will allow us to determine if there is reduced toxicity associated with VMAT compared to SUPR with only a modest impact on resources. Our hypothesis is that VMAT will have reduced toxicity compared with SUPR for palliative patients with bone metastases. We also hypothesize that there will be no difference between the two arms in terms of pain response, due to the fact that the doses are equal. This hypothesis is driven by the radiobiologic rationale, which defines effective RT as the ability of radiation to induce tumour cell death while sparing normal cells.

The importance in determining if there is any benefit in terms of toxicity with VMAT compared with SUPR for palliative patients with bone metastases is obvious when consequences related to its adoption are considered. As previously discussed, although the planning time has been drastically reduced, there is still an expected modest increase in resources required to carry out a VMAT plan. For patients, the pre-treatment process of VMAT is more burdensome, i.e. patients have to wait longer before receiving VMAT as compared to SUPR, due to the increased plan complexity. Therefore, it is important to consider the patient experience in relation to the RT administration.

In summary, evidence that either supports or refutes the hypothesis that VMAT will have reduced toxicity compared with SUPR for patients with bone metastases will be helpful in guiding future practices. We are not aware of any other randomized control trials (completed or ongoing) that have addressed this issue, though a London Ontario study is randomizing patients receiving palliative lung RT to SUPR vs VMAT[9]. Due to the implications of VMAT on departmental resources and patient experience, better evidence from a randomized control trial is required before the widespread use of this technique can be justified.

2.2. Radiation Treatment Overview

2.2.1. Radiation therapy 1 - Simple Unplanned Palliative Radiotherapy (SUPR)

For this study, SUPR refers to the delivery of radiation to the treatment area with a simple technique, either two opposed fields (parallel opposed pair), or a single direct field. The entire portal is exposed to the specified dose and therefore does not spare normal tissue. This technique requires minimal calculation, and typically the dose distribution is not reviewed by the radiation oncologist or medical physics.

Adverse Events (SUPR)

In general, the adverse event profile of RT is associated with irradiation of normal tissue within the treatment field. With the dose prescribed in this study, the probability of serious adverse effects is exceedingly low[10]. However, fatigue, soreness, pain flare, and skin-redness in the irradiated area are relatively common adverse events. In addition, site-specific toxicity could occur, including esophagitis, nausea, or diarrhea when there is dose delivered to the GI tract. Avoiding this toxicity is a motivating factor for the study.

2.2.2. Radiation therapy 2 – Volumetric Modulated Arc Therapy (VMAT)

In order to deliver 3D Conformal Radiotherapy, a CT simulation is used to develop the treatment plan. The goal is to deliver a conformal radiation dose to the target volume with maximal sparing

of the normal tissue. VMAT (Volumetric Modulated Arc Therapy is a type of 3D conformal RT, and delivers the radiation dose more conformally than SUPR, possibly reducing acute and late toxicity[11-13]. The disadvantages of VMAT include more complex planning and quality assurance processes compared with SUPR5. The complex planning required can be time-consuming, which can have a significant impact on departmental resources, and the wait time for the patient.

2.2.3. Sample Collection Schedule

N/A

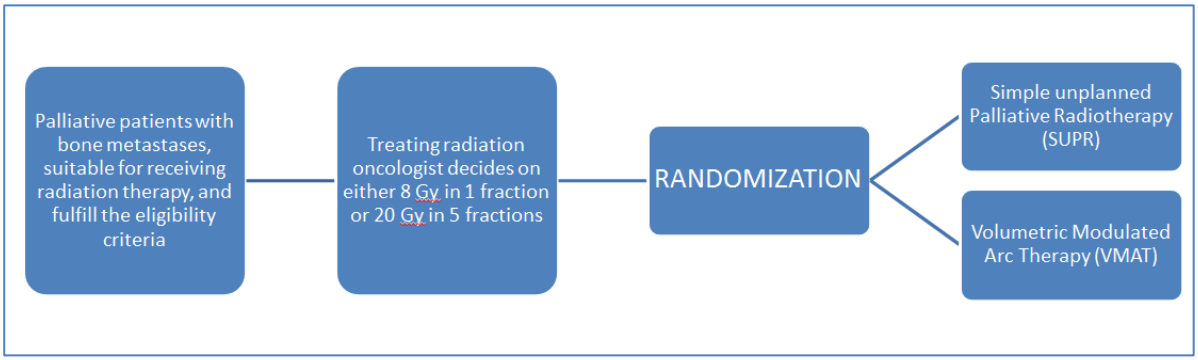
2.3. Study Population

Patients with a clinical diagnosis of bone metastases, meeting all inclusion and exclusion eligibility criteria.

3. Trial Design

This is a randomized, multi-centre, pragmatic phase III study in palliative patients with bone metastases. Randomization will be performed on patient-level, meaning that if a patient is treated for multiple bone metastases in the same course, all will receive the same treatment technique. This applies only to bone lesions, as per section 3.2. Any additional lesions to be treated will be at the RO's discretion.

Patients will be stratified by treatment dose of either 8 Gy in a single fraction or 20 Gy in 5 fractions.



3.1. Study Objectives and Endpoints

3.1.1. Objectives

Primary Objective

The primary objective is to compare patient-reported Quality of Life related to Radiation Induced Nausea and Vomiting (RINV) between standard palliative radiotherapy and VMAT.

Secondary Objective(s)

To assess rate of complete control of RINV, compare patient reported toxicity, and evaluate pain response. However, we hypothesize that there will be no difference in pain response between the two arms, because they are receiving the same dose.

3.1.2. Endpoints

Primary Endpoint:

Patient Reported Quality of life related to Radiation Induced Nausea and Vomiting (RINV) as scored by the Functional Living Index – Emesis (FLIE) at day 5 post RT start.

Secondary Endpoints

Primary efficacy outcome

- Control of RINV measured by a daily patient diary (day 1-5)

Secondary Patient Reported Outcome Measures (PROMs)

- Pain flare measured by the Brief Pain Inventory (BPI)
- Diary of medication use (specifically anti-emetics)
- PRO-CTCAE T11 – L5 & Pelvis:
  - Decreased appetite
  - Nausea
  - Vomiting
  - Diarrhea
  - Radiation skin reaction
  - Pain flare
  - Fatigue
- Pain response assessed by the Brief Pain Inventory.
- Proportion of patients who receive treatment within 1 day, 2 days, 3 days, 4 days, 5 days, or more than 5 days,
- Toxicity assessed at baseline and follow-up
- Quality of Life: single item from EORTC QLQ C-15 PAL: How would you rate your overall quality of life during the past week
- Performance status: as reported by patient with PRO-ECOG
- Cost effectiveness of SUPR vs. VMAT assessed by EQ-5D-5L

3.2. Entry Procedures

PRE-TREATMENT ASSESSMENT

- ECOG status
- Eligibility according to inclusion and exclusion criteria
- Patient Reported Outcomes
  - Brief Pain Inventory
  - Functional Living Index – Emesis
  - EQ-5D-5L

Entry Procedures

All randomizations will be done using a computer-generated randomization scheme.

All eligible patients enrolled in the study by the participating treatment centre will be assigned a study number, which must be used on all documentation.

The following information will be required:

- Trial code (where applicable)
- Name of investigator under whose name the patient will be randomized
- Informed consent, version date, date signed by patient, name of person conducting consent discussion and date signed by the person who conducted the consent from discussion
- Confirmation that the patient meets the eligibility requirements in Section 4.0 (as per completed Subject Registration Form)

Stratification factors

All metastases lying at least partly within T11-L5 or the pelvis will be treated according to randomization technique, and should receive the same dose (either 8 Gy in 1 fraction or 20 Gy in 5 fractions), chosen pre-randomization. All other bone metastases that need to be treated can be treated with either 20 Gy in 5 fractions or 8 Gy in 1 fraction, can be treated at the same time. Technique for these lesions can be chosen by RO or centre discretion. The total number of fields that can be treated synchronously is 3, and included both eligible and ineligible fields. If additional bone metastases are symptomatic, they can be treated at a later time, no sooner than 4 weeks from the end of radiotherapy on trial.

A description of the measures taken to minimize avoid bias including:

a. Randomization (simple/restricted/blocked/stratified)

Simple randomization with stratification will be used to randomly assign patients to either Arm 1 or Arm 2 in a 1:1 ratio using a computer-generated randomization scheme known only to the trial statistician.

b. Blinded/Unblinded

It is not ethically or practically feasible to use double- or single-blinding given the nature of the treatments under investigation. Patients will need to consent to participate in the trial, and treating clinicians and staff will be aware of which patients have been assigned to SUPR versus VMAT. Thus, an open-label randomized controlled study design will be used; however, during interim and final analyses, outcomes assessors and data analysts will be blinded to the identity of each treatment arm to ensure unbiased ascertainment of outcomes. The randomization module was developed, reviewed, and approved by the Study Coordinator and Trial Statistician, and randomization scheme is only known to Coordinator and Statistician, per ICH E9.

3.3. Study Duration

Trial Activities	Start date	End date
Database setup, CRF Development	31-Dec-18	31-Mar-19
Ethics/Site Approvals and Clinical Trial Registration	31-Dec-18	27-Feb-19
Site Training / Initiations	1-May-19	30-Oct-19
Patient Recruitment	1-Aug-19	30-Jun-25
Patient Follow-up	15-Aug-19	30-Aug-25
Safety Analysis	1-May-21	07-Sept-21
Interim Data Analysis (est)	1-Dec-24	31-Jan-25
Database Lock / Final Analyses	30-Aug-25	1-Oct-25
Knowledge Translation (KT) & Evaluation	1-Oct-25	31-Dec-25

4. Eligibility

This study will be offered to all patients presenting with a clinical diagnosis of bone metastases meeting inclusion and exclusion criteria.

Waivers to eligibility criteria are not permitted.

4.1. Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for participation in this study:

- Age 18 or older
- Able to provide informed consent
- Clinical diagnosis of cancer with bone metastases (biopsy not required)
- Currently being managed with palliative intent RT to 1-3 RT fields for bone metastases, at least one RT field (PTV) must (at least) partly lie within T11-L5 or pelvis.
- ECOG Performance Status 0-3
- Patient has been determined to potentially benefit from 8 Gy or 20 Gy
- Radiation Oncologist is comfortable prescribing 8 Gy in 1 fraction or 20 Gy in 5 fractions RT for bone metastases
- Negative pregnancy test result for women of child-bearing potential
- The baseline assessment must be completed within required timelines, prior to randomization.
- Patients must be accessible for treatment and follow-up. Investigators must assure themselves the patients randomized on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.
- For simplicity of planning, expected GTV should be less than 20 cm based on radiological or clinical evidence
- Patient must be prescribed a 5-HT3 receptor antagonist (e.g. Ondansetron) as antiemetic prophylaxis prior to RT start.
- Patient is able and willing to complete the quality of life questionnaires, and other assessments that are a part of this study, via paper or using REDCap if they provide their email address on the informed consent

4.2. Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

- Serious medical co-morbidities precluding radiotherapy
- Clinical evidence of spinal cord compression
- Spinal cord in treatment field has already received at least >30 Gy EQD2, defined as:
  $EQD_2 = D \times ([d + (\alpha/\beta)]/[2 + (\alpha/\beta)])$
  D = total dose given in Gy
  d = dose per fraction in Gy
  α/β = dose at which the linear and quadratic components of cell kill are equal
- Whole brain radiotherapy (WBRT) within 4 weeks of RT start or planned WBRT in the first 4 weeks after last RT
- Solitary plasmacytoma
- Pregnant or lactating women
- Target volume cannot be encompassed by a single VMAT isocentre
- Custom mould room requirements (shells and other immobilization that is standard-of-care is acceptable)
- Greater than two organs-at-risk requiring optimization.
- Patients requiring treatments outside standard clinical hours
- Implanted electronic device within 10 cm of the RT fields
- Prostheses in the axial plane of the target, or within 1 cm of the PTV out-of-plane
- Previous RT that requires an analysis of cumulative dose (i.e. sum plans or EQD2 calculations)
- Oral or IV contrast if the local standard-of-care requires compensation for this in planning.

4.3. Subject Withdrawal Criteria

Subjects may voluntarily discontinue participation in the study at any time.

If a subject is withdrawn from the study, the assessments and evaluations that would have been performed at the Study Completion/Early Termination (see Section 4.8) should be obtained, if the patient is willing. The SUPR-3D Participant Withdrawal form should also be completed in addition to completion of the Study Termination form in REDCap.

Subjects withdrawn or discontinued can be replaced at the discretion of the sponsor-investigator/Study Principal Investigator.

If a subject is removed because of an adverse or serious event, they should remain under medical observation as long as deemed appropriate by the treating physician, and follow recording and reporting requirements listed in Section 8.2.

4.3.1. Informed Consent

The written informed consent form must be approved by the IRB/REB and adhere to ICH GCP and the ethical principles that have their origin in the Declaration of Helsinki.

The investigator is responsible for obtaining written informed consent from each subject, or if the subject is unable to provide informed consent, the subject's legally acceptable representative, prior to beginning any study procedures and treatment(s). The investigator should inform the subject, or the subject's legally acceptable representative, of all aspects of the study, including the potential risks and benefits involved.

All screening evaluations must be completed and reviewed to confirm that subjects meet all eligibility criteria prior to study enrollment. A screening log will be maintained to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

The subject should be given ample time and opportunity to ask questions prior to deciding about participating in the study and be informed that participation in the study is voluntary and that they are completely free to refuse to enter the study or to withdraw from it at any time, for any reason. The informed consent must be signed and dated by the subject, or the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

A copy of the signed and dated written informed consent form should be given to the subject or the subject's legally acceptable representative. The process of obtaining informed consent should be documented in the patient source documents using the PRO-FRM-013: Documentation of Informed Consent. See Section 12.1.3 for detailed information on informed consent process.

4.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened Subjects should be assigned the same subject number as for the initial screening.

4.5. Availability for Follow-up

Patients must be accessible for treatment and follow-up. Investigators must assure themselves the patients randomized on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

4.6. Ability to tolerate current treatment

Patients must be able to maintain a stable position to tolerate SUPR or VMAT.

4.7. Biopsy/Tissue/Blood banking

N/A

4.8 Schedule of Assessments

Assessment	Screening: Visit-1	Baseline, Enrollment, Randomization: Visit 1	Treatment: Visit 2 (Day 1)	Treatment / Follow-Up (for 8Gy/1# patients) Visit 3 (Day 5)	Follow-Up Visit 4 (W2 post last RT) +/- 3 days	Follow-Up Final Visit (W4 post last RT) +/- 3 days
Informed Consent	X					
Inclusion/Exclusion Criteria	X					
Enrollment/ Randomization		X				
*Medical History/ Comorbidities	X					
Physical Examination	X					
€Pregnancy Test	X					
Patient Diary (provided to patient)			X	X		
**Brief Pain Inventory		X	X		X	X
**Functional Living Index - Emesis		X	X	X	X	X
PROMS		X	X		X	X
Treatment Related Data			X			
***Baseline & Follow-up		X	X		X	X
EQ-5D-5L		X			X	X

*may be done within 90 days, or 3 months, prior to enrollment

**BPI, FLIE and PROMS on Day 1 does not need to be repeated if collection was done within 7 days of first treatment (day 1).

***Baseline & Follow-up form does not need to be repeated if collection was done within 2 days of first treatment (day 1). If RT starts 3 or more days after baseline collection, or anytime medication changes (if known), this form will need to be repeated

€Urinalysis or serology – per institutional guidelines.

4.8.1 Investigations Prior to Randomization/Study Entry, During Trial and Follow-up

Physical and Medical History will be valid within 6 weeks prior to enrollment.

Pregnancy test results will be valid for 4 weeks prior to treatment.

5. Subject Treatment Plan

5.1. Trial Treatment Summary

5.1.1. ARM 1 - SUPR

Radiation Treatment Plan for SUPR (Arm 1)

- Planning according to local protocols.
- No more than 2 fields; no beam modifying devices, other than multileaf collimators (MLCs). Alternate weighting of beams allowed (ie. 1:2 AP:PA). Review of dosimetry not required, if performed as per institutional standard.
- Minimum of kV image matching on unit daily.

5.1.2. ARM 2 - VMAT

Radiation Treatment Plan for VMAT rapid (Arm 2)

Contouring:

GTV: based on available imaging (GTV may be based on CT sim scan alone. No special imaging) and is expected to be between 1.5 cm and 20 cm clinically or from diagnostic imaging

CTV is optional in all scenarios: when using CTV = GTV + 0.5 to 0.7 cm (RO preference), adjusted to the anatomy as further outlined below.

- In case of only bone involvement: recommendation is **not** to expand past bone; however, a 0.5 – 0.7 cm CTV expansion outside of bone and into muscle or soft tissue is allowed at the treating RO's discretion.
- In case of bone and soft tissue involvement: a 0.5 to 0.7 cm CTV expansion is optional and allowed at RO's discretion.
- In case of spinal metastases: CTV is optional and if used can encompasses whole vertebral body as per RO's discretion

PTV = CTV or GTV (if CTV not used) + (1 to 1.5) cm as per RO / centre preference.

PTV_eval = PTV cropped 0.5 cm below skin.

OAR's: A maximum of 2 OAR's are permitted for the VMAT arm. OAR contouring and constraints are at the discretion of the treating RO. However, if lung/kidneys are within 5 cm of the PTV, the absence of constraints for these contours should be documented in the treatment plans or dose constraint sheet prior to planning. PTV can be compromised for OAR at radiation oncologist's discretion. Kidneys are considered 1 organ.

Planning:

- AAA or other type-2 / model-based calculation framework
- Heterogeneities on
- Maximum calculation grid size = 2.5 mm
- Planning VMAT flash is permitted but not required
- Jaw-tracking is permitted but not required
- A normal tissue constraint should be used to control conformity to at least the 65% isodose level
- For the VMAT arm, up to two arcs are permitted
- The 80% conformity index (CI).

Required Constraints:

- PTV / PTV_eval coverage: The volume of the PTV covered by the 95% isodose volume must be greater than or equal to 98% (V95% ≥ 98%). (V95%< 98% minor violation; V95% <50% major violation).
- The 80% conformity index (CI), being the ratio of the 80% isodose volume to the PTV volume, must be less than 1.75 (1.75 - 1.9 minor violation; > 1.9 major violation)
- Plan maximum dose (Dmax) = 110% (> 110% but ≤ 115% minor violation; > 115% major violation)
- Maximum of 2 constrained OAR's
- In case of accomplished constraints for CI, Dmax and OAR's (if present): no further plan modification permitted by RO

Suggested Constraints

Recommended OAR constraints are given on the table below, which are based on QUANTEC, adapted to the specific dose per fraction of the two schedules. The decision to include or adjust these constraints is at the discretion of the RO.

	8 Gy in 1 fraction	20 Gy in 5 fractions
*Spinal Cord (PRV)	Max dose < 110% of 8 Gy	Max dose < 110% of 20 Gy
Lungs (excl. GTV)	V6 Gy < 35%	V12 Gy < 35%
	Mean dose < 6 Gy	Mean dose < 12 Gy
Kidney (each)	V6 Gy < 30%	V12 < 30%
	Mean dose < 5 Gy	Mean dose < 10 Gy
**Small Bowel	Max dose < 110% of 8 Gy	Max dose < 110% of 20 Gy

** spinal cord to L2, spinal cord PRV is 0.5 cm margin around the spinal cord*
*** small bowel contoured by RO or RT depending on institutional polices*

Plan Review and QA:

No pre-treatment dosimetric review is required if both the required and specified OAR constraints are met. Otherwise, the plan must be reviewed by the RO prior to treatment. Document any further plan modification secondary to subsequent local QA procedures as a minor protocol violation. Physics and dosimetry checks are to be performed as per local standard-of-care.

Verification Imaging:

IGRT: Minimum IGRT is daily 2D kV matching. CBCT is not required but may be used at the discretion of the treating radiation oncologist

Quality Assurance

Dosimetric compliance with protocol constraints will be evaluated by the planning dosimetrist(s) and physicist(s). Plan review by the radiation oncologist is not required for both arms. The radiation oncologist might review the plan but no plan modification at that point is permitted.

For VMAT, patient-specific QA should be performed per standard processes.

Institutional quality assurance rounds may also evaluate the radiation plans.

5.1.3. Duration of Study

The study is expected to be 7 years, as per section 3.3

5.2. Data Handling and Recordkeeping

- All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, REB review, and regulatory agency inspections and provide direct access to source data documents.

- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the SUPR-3D Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of Subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be sent to the Study Principal Investigator (SPI) for long-term storage and will be retained by the SPI for 25 years after study completion. No records may be destroyed during the trial and/or retention period. No records may be transferred to another location or party without written notification to the sponsor.

5.2.1. Subject Reported Outcomes – Questionnaires

5.2.1.1. Functional Living Index – Emesis

To assesses primary efficacy outcome - Patient Reported Quality of life related to Radiation Induced Nausea and Vomiting (RINV), as scored by the FLIE at day 5 post RT start. Electronic or Paper both available.

5.2.1.2. Brief Pain Inventory

To assess pain flare and response. Electronic and Paper both available.

5.2.1.3. Patient Diary

To assess control of RINV and medication use. Paper version only will be provided to patient.

5.2.1.4. PROMS Questionnaire

Patient reported, combined questionnaire including:

- Single item from EORTC QLQ C-15 PAL (How would you rate your overall quality of life during the past week?) to assess overall quality of life
- PRO-CTCAE to assess fatigue and skin burn
- PRO-ECOG to assess functional status

Electronic or Paper both available.

5.2.1.5 EQ-5D-5L

To capture patient-reported Health-Related Quality of Life (HRQoL), scores from which will be used to inform cost effectiveness analysis of SUPR vs. VMAT.

5.2.1.6 Baseline Symptoms and Post-Treatment Toxicity

Baseline Symptoms and Post-Treatment Toxicity assessed by care provider at baseline and follow-up.

5.2.2 Records Retention

Records and documents, including signed ICFs, pertaining to the conduct of this study must be sent to the Study Principal Investigator (SPI) for long-term storage and will be retained by the SPI for 15 years after study completion. No records may be destroyed during the trial and/or retention period. No records may be transferred to another location or party without written notification to the sponsor.

5.3. Lifestyle Considerations, Prohibited Food and Additional Restrictions

5.3.1. Required Therapy

All patients will receive a 5HT-3 receptor antagonist (e.g. Ondansetron) as antiemetic prophylaxis prior to RT start

5.3.2. Permitted Concomitant Therapy

Nausea prophylaxis

Dexamethasone may be given for nausea prevention, though is not mandated.

Analgesics

Analgesics are allowed to be prescribed as needed by the patient to obtain optimal pain control.

Concurrent hormonal therapy

Concurrent receipt of hormonal therapy is allowed during this study.

5.3.3. Prohibited Concomitant Therapy

Use of the following concomitant therapies is prohibited as described below:

- Use of chemotherapy schemes containing potent enhancers of radiation damage (e.g. gemcitabine, doxorubicin, bevacizumab, adriamycin) are **discouraged within the first month after radiation**.
- WBRT in the 4 weeks before first RT and 4 weeks after last RT
- SFRT for brain metastases in the 4 weeks after last RT

5.3.4. Herbal Therapies

Concomitant herbal therapies that the subject is using do not need to be recorded.

5.3.5. Data for Concomitant Medications

Concomitant medications must be recorded on the SUPR-3D concomitant medication form, which is a cumulative form to be updated throughout the study.

If no concomitant medications are being taken at the time of study visits, this can be indicated on a line on the form, with the following annotation:

'Confirmed no concomitant medications are being taken during study visit X [Date: DD MMM YYYY; INITIALS]'

5.4. Co-enrolment and/or Re-enrolment

Enrolment in other studies **may** be permitted. Investigators **must** check with study principal investigator.

Patients who have participated in the SUPR-3D trial previously, and completed all study visits, may be eligible for re-enrolment in to SUPR-3D. Sites must check with either the Site PI or Study PI regarding re-enrolment as all eligibility criteria must be met for the re-enrolment. Re-enrolled patients must be assigned a new study ID (treat as if new enrollment).

5.5. Subject Compliance/Deviations

Subject compliance, such as attending study visits and completing questionnaires, will be monitored via REDCap. If any visits are not completed, investigator or delegate must call and conduct follow-up over the telephone. Missed visits must be documented in the deviation log.

Deviations to eliminate immediate hazards to study subjects must be reported to the Study PI immediately upon discovery and to the REB within 7 calendar days. All other reportable deviations must be reported to the Study PI immediately, however to the REB within 15 calendar days. See section **12.1.2 Protocol Deviations** for a list of deviations.

6. Dose Modifications

N/A.

7. Assessment of Efficacy

Treatment Response Evaluation

FLIE:

Scores on all individual questions will be weighted equally, reversed if required and summed to create an overall FLIE score. Minimum score and maximum score will be 18 and 126 respectively. A low score is favorable, reflecting less nausea and vomiting.

The paper version of the FLIE is a 7-point Likert-scale. Patients' responses will be rounded to the closest point on the scale for entry in the digital database. I.e. if the response is 1.4, this will be rounded to 1. If the response is 1.5, it will be rounded to 2.

RINV:

Complete control: no increased episodes of nausea or vomiting with no increased use of anti-emetic medication from baseline

Partial control: 1-2 increased episodes of nausea or vomiting with no increased use of anti-emetic medication compared to baseline

Uncontrolled response: 3 or more increased episodes of nausea or vomiting, or increased use of anti-emetic medication from baseline

Overall control: includes complete and partial control

Pain:

Complete response: pain score of 0 at treated site with no increase in analgesic intake (stable or reducing analgesics in daily oral morphine equivalent (OMED).

Partial response: pain reduction of 2 or more at the treated site on a scale of 0 to 10 without analgesic increase, or analgesic reduction of 25% or more from baseline without an increase in pain.

Pain progression: Increase in pain score of 2 or more above baseline at the treated site with stable OMED, or an increase of 25% or more in OMED compared with baseline with the pain score stable or 1 point above baseline.

Indeterminate response: Any response that is not captured by the complete response, partial response or pain progression definitions[14].

8. Assessment of Safety

8.1 Specification of Safety Parameters

8.2 Recording and Reporting of Adverse Events (AEs)

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or Serious Adverse Event (SAE) and remain responsible for following up on AEs that are serious, considered related to the study intervention or study procedures, or that caused the subject to discontinue the study treatment or participation in the study.

8.2.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from the start of intervention until completion of all follow-up visits.

All SAEs will be collected from the start of intervention until completion of all follow-up visits.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent must be recorded in the subject's medical record.

8.2.2 Method for Detecting AEs and SAEs

Definitions
An *Adverse Event (AE)* is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure.

Serious Adverse Event (SAE) as defined in the ICH Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, E2A Section IIB includes any untoward medical occurrence that at any dose/treatment:

- Results in death
- Is life-threatening (refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)
- Results in persistent or significant disability/incapacity
- Requires in-patient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for scheduled elective surgery and admissions for palliative or terminal care)

- Is a congenital anomaly/birth defect

Important medical events that may not be immediately life-threatening or result in death or hospitalization may be considered a serious adverse event, when, based upon medical and scientific judgment, they may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Unanticipated/unexpected events include events that are inconsistent with, or present a greater risk of harm, than the known or recognized risks or side effects of SUPR or VMAT treatment as explained to the patient under standard of care. Unanticipated events also include those events where there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research (i.e. possibly, probably, or definitely related to participation in the research itself).

Expected events are distinguished from unexpected events on a case by case basis, at the discretion of the radiation oncologist.

Causality

An adverse event is considered **related** to the research intervention if there is a reasonable possibility that the event may have been caused by the research intervention (i.e. a causal relationship between the event and the research intervention cannot be ruled out by the investigator(s)).

The relationship of an AE to the study treatment (causality) will be described using the following definitions:

Unrelated: Any adverse event for which there is evidence that an alternative etiology exists or for which no timely relationship exists to the administration of the study treatment and the adverse event does not follow any previously documented pattern. The adverse event, after careful consideration by the investigator, is clearly and incontrovertibly due to causes other than the intervention.

Unlikely: Any adverse event for which the time relationship between the study treatment and the event suggests that a causal relationship is unlikely and/or the event is more likely due to the subject's clinical condition or other therapies concomitantly administered to the subject.

Possible: Any adverse event occurring in a timely manner after the administration of the study treatment that follows a known pattern to the intervention and for which no other explanation is

known. The adverse event, after careful consideration by the investigator, is considered to be possibly related and cannot be ruled out with certainty.

Probable: Any adverse event occurring in a timely manner after the administration of the study treatment that follows a known pattern to the intervention and for which no other explanation is known. The adverse event, after careful consideration by the investigator, is believed with a high degree of certainty to be related to the intervention.

Definitely Related: Any adverse event occurring within a timely manner after administration of the study treatment that is a known sequela of the intervention and follows a previously documented pattern but for which no other explanation is known. The adverse event is believed by the investigator to be incontrovertibly related to the intervention.

Severity

The severity of adverse events will be evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 grading scale[15].

Grade 1: Mild
Grade 2: Moderate
Grade 3: Severe
Grade 4: Life-threatening or disabling
Grade 5: Death

Grade 1 toxicities such as mild fatigue, nausea, vomiting, skin irritation, pain, loss of appetite and some physical function are common and expected side effects of radiation therapy and therefore should not be reported as adverse events, if the event is documented in the subject's medical record[16]**. Only Grade 2 or higher toxicities that are relevant to treatment-related area(s) will be documented as AEs/SAEs for both treatment arms**.

These toxicities must be documented in the AE log and SAE report form, and entered in REDCap, and follow REB and institutional reporting guidelines.

Note: The term "severe" is a measure of intensity: thus a severe adverse event is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

Immediately Reportable Serious/Adverse Events

Any **Grade 4 or 5 serious adverse event** that is definitely, probably, or possibly the result of protocol treatment must be reported to the Study PI within 24 hours of discovery, and

further reported to the REB per institutional guidelines. The follow-up/final report should be completed within an additional 8 days. All other SAEs (Grade 2-3) that are definitely, probably, or possibly related to treatment should be reported to the Study PI within 15 days. These should be documented in an SAE Report form and in REDCap as well.

Unanticipated events are to be reported to the Study PI within 24 hours of discovery, and to the local REB as required.

Local and non-local SAEs will be reported to the applicable REB as per their reporting guidelines.

NOTE: Conditions that are NOT considered a SAE in this protocol are not included in reporting requirements, e.g., hospitalizations for routine procedures, disease progression, or death from disease progression

8.3 Follow-up of Subjects after Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 11.5).

8.4 Pregnancy

Details of pregnancies will not be collected.

9. Statistics

9.1. Statistical Methods

Patients will be analyzed in the groups to which they are assigned (intention-to-treat). All analyses will be done using t-tests between the average scores of the two arms.

RINV will be assessed via Functional Living Index – Emesis (FLIE) scores compared between the two arms at baseline and day 5 post start of RT

Health-Related Quality of Life (HRQoL) will be measured using the EQ-5D-5L and combined with survival outcomes to explore differences in Quality Adjusted Life Year (QALY) gains or losses between treatments

9.2. Planned Subjects Enrolled

The primary outcome is Functional Living Index – Emesis (FLIE) score compared between the two arms at day 5 post start of RT. We expect patients in the SUPR arm to have a mean FLIE score of 36, 5 days post start of RT[17]. We anticipate that VMAT will have a much lower RINV impact (i.e. less decline in FLIE) and for the purpose of this study will hypothesize that the FLIE will be approximately 28. The standard deviation used for sample size calculation was 16.

Sample size was calculated with these FLIE scores. With alpha Type I error set at 0.05 and power set at 0.9, with a dropout rate of 30%, we calculated a conservative sample size of 250 patients. This dropout rate of 30% is a conservative number. We will collect patient demographics and if there is an indication that bias is being introduced because of dropout, we will consult with a statistician.

Our most important secondary outcome (primary efficacy outcome) is radiation induced nausea and vomiting (RINV) which occurs in 60% of patients who receive RT to the lower spine or pelvis[17, 18]. Using the sample size of 250 patients (see above), this study has a power of 0.8 to detect a 25% difference in RINV (from 60% to 35%) with alpha Type I error set at 0.05 and a dropout rate of 20%. As outlined in the table below, if RINV difference is lower, or higher our power will be lower and higher, respectively.

Health-Related Quality of Life (HRQoL) will be measured using the EQ-5D-5L and combined with survival outcomes to explore differences in Quality Adjusted Life Year (QALY) gains or losses between treatments[19].

Approximate sample size required

RINV 60% to 50%	1600
RINV 60% to 40%	400

RINV 60% to 35%	250
RINV 60% to 30%	175
RINV 60% to 20%	90

9.3. Procedures for Reporting Deviations from the Statistical Plan

Any deviations from the original statistical plan should be described and justified in progress and/or in the final report, as appropriate.

10. Measurement of Study Endpoints

10.1. Definitions

10.1.1. Patient Reported Quality of life

Related to Radiation Induced Nausea and Vomiting (RINV) as scored by the Functional Living Index – Emesis (FLIE) at 5 days post RT start.

10.1.2. Toxicity

Toxicity assessed at baseline and follow-up

10.1.3. Health-Related Quality of Life (HRQoL)

Measured using the EQ-5D-5L and combined with survival outcomes to explore differences in Quality Adjusted Life Year (QALY) gains or losses between treatments18.

Primary efficacy outcome

- Control of RINV measured by a daily patient diary (day 1-5)

Secondary Patient Reported Outcomes

- Pain flare measured by the **Brief Pain Inventory (BPI)**
- **Diary** of medication use (specifically anti-emetics)
- Fatigue (**PRO-CTCAE**)
- ECOG

- **PRO-CTCAE T11 – L5 & Pelvis:**
  - Decreased appetite
  - Nausea
  - Vomiting
  - Diarrhea
  - Radiation skin reaction

  - Pain flare
  - Fatigue
- Pain response assessed by the Brief Pain Inventory.
- Proportion of patients who receive treatment within 1 day, 2 days, 3 days, 4 days, 5 days, or more than 5 days

Phases of Treatment

Early phase: day 1 of radiation treatment to day 1 post-treatment

Delayed phase: days 2-5 post-treatment

10.2. Evidence of Disease Recurrence

Disease recurrence will not be monitored.

10.3. Dating of First Recurrence

N/A

10.4. Management Following Recurrence

N/A

11. Discontinuation of Trial and Subject Discontinuation/Withdrawal

11.1. End of Study Definition

A subject is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities.

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Activities for the last subject in the trial globally.

11.2. Discontinuation of trial

If the DSMC deems that toxicity rates are excessive (>25% grade 3 toxicity, or >10% grade 4 or >3% 5 toxicity), then the DSMC can, at its discretion, recommend cessation of the trial, dose adjustment, or exclusion of certain treatment sites that are deemed as high-risk for complications.

11.3. Subject Discontinuation/Withdrawal from the Study

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, etc. reasons.

At the time of discontinuing from the study, if possible, an early discontinuation/termination visit should be conducted. See Section 4.8 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The date and reason for Subject discontinuation must be recorded on the Study Termination form in REDCap.

11.4. Post-Trial Follow-up

There is no planned follow-up at the end of the study. Any additional care that will be provided to Subjects after they complete or discontinue the study will involve standard of care treatment for what is normally expected for their condition.

11.5. Lost to Follow up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

12. Regulatory, Ethical, and Study Oversight Considerations

The Principal Investigators will obtain ethical approval and clinical trial authorization by competent authorities according to local laws and regulations.

12.1. Regulatory and Ethical Considerations

12.1.1. REB (Research Ethics Board) Approvals for Protocols (change as needed)

This study will be conducted in accordance with the protocol and with the following:

- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations.

The protocol (and any amendments), the informed consent form, and any other written information to be given to subjects will be reviewed and approved by a properly constituted Institutional Review Board (IRB)/Research Ethics Board (REB), operating in accordance with the current federal regulations ICH GCP and local regulatory requirements. A letter to the investigator documenting the date of the approval of the protocol and informed consent form will be obtained from the IRB/REB prior to initiating the study. Any institution opening this study will obtain IRB/REB approval prior to local initiation and will be responsible for maintaining approval throughout the duration of the trial. Principal Investigators must provide evidence of IRB/REB approval on an annual basis.

The Study Principal Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the REB annually or more frequently in accordance with the requirements, policies, and procedures established by the REB
- Notifying the REB of SAEs and unanticipated problems or other significant safety findings as required by REB procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the REB and all other applicable local regulations

Participating sites must receive pre-approval from the Study Principal Investigator for any amendments to the protocol.

12.1.2. Protocol Deviations

A protocol deviation occurs when the subject, investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol deviations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication
- Failure to comply with OAR constraints
- Failure to comply with treatment dose, fractionations, constraints and/or frequency as specified in this protocol
- Failure to conduct study follow-up visits and/or to collect study-related data within the timeframes as specified in this protocol

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol deviation. The Sponsor will determine if a protocol deviation will result in withdrawal of a subject.

When a protocol deviation occurs, it must be documented on the Protocol Deviation Log in REDCap. The deviation will be discussed with the investigator and a Protocol Deviation Report detailing the deviation may be requested. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files. The deviation may also require further reporting to the REB per BC Cancer SOPs

12.1.3. Informed Consent Process

The investigator or delegate will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, applicable and the REB or study center.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign and date the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

12.1.4. Data Protection

Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate REB members, and by inspectors from regulatory authorities.

12.1.5. Committees Structure

There is no independent data safety monitoring committee (DSMC) for this study. The DMSC will be made up of the study co-investigators. The DSMC will meet annually after study initiation to review toxicity outcomes. If any grade 3-5 toxicity is reported, the DSMC will review the case notes to determine if such toxicity is related to treatment.

12.1.6. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of subjects.

BC Cancer reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the REB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of Subjects by the investigator

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the REBs, and regulatory authorities as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

12.1.7. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements

12.2. Financial Support

This trial is funded by the BC Cancer Research Foundation and Varian Medical Systems. The funding agencies are not directly involved in data collection or analysis.

12.3. Trial Management

The Coordinating Centre for this study will be BC Cancer-Prince George under leadership of Dr. Robert Olson as Study Principal Investigator. Dr. Olson and the Coordinating Centre will be responsible for trial activities at all participating sites, including international sites. The Coordinating Centre will be responsible for randomization of participants using a randomization module in the REDCap Electronic Data Capture (EDC) system which will be used for trial data collection. In conjunction with trial statistician and Site Principal Investigators, the Coordinating Centre will be responsible for storing and analyzing trial data. Designated Site Principal Investigators will be responsible for reviewing eligibility of participants at their centre. In addition to providing credentials, evidence of regulatory training, and evidence of IRB/REB approval, all sites will receive protocol training and data entry training prior to site initiations.

13. REFERENCES

1. Chow E, Zeng L, Salvo N, et al: Update on the systematic review of palliative radiotherapy trials for bone metastases. Clin Oncol (R Coll Radiol) 24:112-124, 2012

2. Lutz S, Berk L, Chang E, et al: Palliative radiotherapy for bone metastases: An ASTRO evidence-based guideline. Int J Radiat Oncol Biol Phys 79:965-976, 2011

3. Nielsen OS: Palliative radiotherapy of bone metastases: There is now evidence for the use of single fractions. Radiother Oncol 52:95-96, 1999

4. Chow E, Hahn CA, Lutz ST: Global reluctance to practice evidence-based medicine continues in the treatment of uncomplicated painful bone metastases despite level 1 evidence and practice guidelines. Int J Radiat Oncol Biol Phys 83:1-2, 2012

5. van der Linden, Yvette M, Steenland E, van Houwelingen HC, et al: Patients with a favourable prognosis are equally palliated with single and multiple fraction radiotherapy: Results on survival in the dutch bone metastasis study. Radiother Oncol 78:245-253, 2006

6. Zeng L, Chow E, Bedard G, et al: Quality of life after palliative radiation therapy for patients with painful bone metastases: Results of an international study validating the EORTC QLQ-BM22. Int J Radiat Oncol Biol Phys 84:337, 2012

7. Olsen JR, Parikh PJ, Hunt S, et al: Sequential short course radiation and FOLFOX as preoperative therapy for rectal cancer: Favorable LC, PFS, and QOL at 2 years. International Journal of Radiation Oncology, Biology, Physics 87:S88, 2013

8. Vanetti E, Nicolini G, Nord J, et al: On the role of the optimization algorithm of RapidArc(®) volumetric modulated arc therapy on plan quality and efficiency. Med Phys 38:5844-5856, 2011

9. Louie A, Gratton A: A randomized phase III study of palliative radiation of advanced central tumors with intentional avoidance of the esophagus - full text view - ClinicalTrials.govhttps://clinicaltrials.gov/ct2/show/NCT02752126

10. Sahgal A: Study comparing stereotactic body radiotherapy vs conventional palliative radiotherapy (CRT) for spinal metastases - full text view - ClinicalTrials.govhttps://clinicaltrials.gov/ct2/show/NCT02512965

11. Teoh M, Clark CH, Wood K, et al: Volumetric modulated arc therapy: A review of current literature and clinical use in practice. The British Journal of Radiology 84:967, 2011

12. Webb S: Advances in treatment with intensity-modulated conformal radiotherapy. Tumori 84:112-126, 1998

13. Guerrero Urbano MT, Nutting CM: Clinical use of intensity-modulated radiotherapy: Part I. Br J Radiol 77:88-96, 2004

14. Chow, Edward, M.B.B.S.|Hoskin, Peter, M.D.|Mitera, Gunita, Ph.D.(C)|Zeng, Liang, B.Sc.(C)|Lutz, Stephen, M.D.|Roos, Daniel, M.D.|Hahn, Carol, M.D.|van der Linden, Yvette, M.D.|Hartsell, William, M.D.|Kumar, Eshwar, M.B.B.S: Update of the international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. International Journal of Radiation Oncology, Biology, Physics 82:1730-1737, 2012

15. National Cancer Institute: Common terminology criteria for adverse events (CTCAE) v4.0 . , 2017

16. Jamal-Hanjani M, Wilson GA, McGranahan N, et al: Tracking the evolution of Non–Small-cell lung cancer. The New England Journal of Medicine 376:2109-2121, 2017

17. Dennis K, Nguyen J, Presutti R, et al: Prophylaxis of radiotherapy-induced nausea and vomiting in the palliative treatment of bone metastases. Support Care Cancer 20:1673-1678, 2012

18. Feyer P, Maranzano E, Molassiotis A, et al: Radiotherapy-induced nausea and vomiting (RINV): MASCC/ESMO guideline for antiemetics in radiotherapy: Update 2009. Support Care Cancer 19:5-14, 2011

19. Krabbe PFM: Editorial: The development of new research methods for the valuation of EQ-5D-5L. 14:1-3, 2013

APPENDIX A – ELIGIBILITY CRITERIA

Eligibility Checklist

You must be able to circle Y (Yes) to all of the following:

Y / N : Age 18 or older

Y / N: Able to provide informed consent

Y / N: Clinical Diagnosis of cancer with bone metastases

Y / N: Currently being managed with palliative intent RT to 1-3 RT fields for bone metastases, at least one RT field (PTV) must (at least partly) lie within T11-L5 or pelvis

Y / N: ECOG Performance Status 0-3

Y / N: Radiation Oncologist is comfortable prescribing 8 Gy in 1 fraction or 20 Gy in 5 fractions RT for bone metastases

Y / N: Patient has been determined to potentially benefit from 8 Gy or 20 Gy

Y / N / NA: Negative pregnancy test result for women of child-bearing potential

Y / N: Patients must be accessible for treatment and follow-up

Y / N: Radiological or clinical evidence confirming GTV is expected to be less than 20 cm

Y / N: Patient will be/has been prescribed a 5HT-3 receptor antagonist (e.g. Ondansetron) as antiemetic prophylaxis prior to RT start.

Y / N: Patient is able and willing to complete the quality of life questionnaires, and other assessments that are a part of this study, via paper or using REDCap if they provide their email address on the informed consent

Exclusion Criteria

You must be able to circle N (No) to all of the following:

Y / N: Serious medical co-morbidities precluding radiotherapy

Y / N: Clinical or radiological evidence of spinal cord compression

Y / N: Solitary plasmacytoma

Y / N: Pregnant or lactating women

Y / N: Target volume cannot be encompassed by a single VMAT isocentre

Y / N: Custom mould room requirements (shells and other immobilization that is standard-of-care is acceptable)

Y / N: Greater than two organs-at-risk requiring optimization.

Y / N: Spinal cord in treatment field has already received at least >30 Gy EQD2

Y / N: Whole brain radiotherapy (WBRT) within 4 weeks of RT start and planned WBRT in the 4 weeks after last RT

Y / N: Implanted electronic device within 10 cm of the RT fields

Y / N: Prostheses in the axial plane of the target, or within 1 cm of the PTV out-of-plane

Y / N: Previous RT that requires an analysis of cumulative dose (i.e. sum plans or EQD2 calculations)

Y / N: Oral or IV contrast if the local standard-of-care requires compensation for this in planning.

Y / N: Patient requires treatment outside standard clinical hours

Protocol Signature Page

Protocol Title: SUPR-3D: A RANDOMIZED PHASE III TRIAL COMPARING SIMPLE UNPLANNED PALLIATIVE RADIOTHERAPY VERSUS 3D CONFORMAL RADIOTHERAPY FOR PATIENTS WITH BONE METASTASES

Protocol Version/ Date: v12.0; 16 Apr 2024

Sponsor/Study Principal Investigator Name: Dr. Robert Olson

Site: _____

Declaration of Investigator

I agree to:

- conduct the described trial in compliance with all stipulations of the protocol and ICH E6 Guideline for Good Clinical Practice (GCP);
- comply with procedures for data entry/recording/reporting as outlined in the data management plan;
- permit monitoring, auditing and inspection; and
- retain the trial related essential documents until Dr. Robert Olson (Study Principal Investigator) informs me that these documents are no longer needed.

Site Principal Investigator Name: _____

Site Principal Investigator Signature: _____

Date: _____